

## *Testosterone Therapy Does Not Raise Heart Risk in a Group of Men*

New results from a large study are reassuring, but questions remain about long-term safety, and about use by men without medical conditions.



By Roni Caryn Rabin

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The largest study ever done to evaluate the safety of hormone replacement for men has reassuring news for a limited group of patients whose bodies don't produce enough testosterone, finding that the hormone does not increase heart attacks, strokes and cardiac deaths.

The new results, which come from a large clinical trial of the kind considered the gold standard in medicine, do not put all concerns to rest. But they appear to resolve decades of contradictory findings about the heart safety of testosterone treatment for men who have a medical condition called androgen deficiency, or hypogonadism.

The authors emphasized that the results did not apply to the many men who are middle-aged and older who take testosterone offered at anti-aging centers in hopes of building muscle or boosting their energy and sex drive, often without being properly evaluated. Instead, it pertains only to the small percentage of the country's male population, believed to be in the low single digits, with a true medical diagnosis of hypogonadism, or with consistently low testosterone levels and symptoms that may include osteoporosis and anemia as well as low libido.

"We have never had a study of more than 5,000 men followed up to four years, with their heart attacks and strokes carefully tracked," said Dr. Bradley Anawalt, an endocrinologist and professor of medicine at the University of Washington School of Medicine who was not involved in the trial.

“The important caveat is that this should not be interpreted as saying that testosterone does not cause heart attacks and strokes in men without hypogonadism,” he said. “It is not a signal that testosterone is safe to take in high amounts, for normal men.”

While testosterone levels tend to decline with age, as well as with weight gain, true hypogonadism is believed to be much less common, according to the authors of the study, and experts say the prevalence and incidence have not been well studied.

The study enrolled 5,246 men all over the United States aged 45 to 80 with the diagnosis, and randomly assigned them to receive a patch with either a standard dose of testosterone or a placebo with no active ingredient. All of the men had heart disease or were at high risk for it. But after an average of two years of follow-up, researchers found that testosterone had not increased their risk of heart attacks, strokes or other heart disease deaths.

Some 7 percent of the men in each group experienced a heart event of some kind during the follow-up period — whether they were on testosterone or not.

But the study identified other potentially serious complications that occurred at low rates among patients who received the treatment, including a higher risk of acute kidney disease, blood clots in vessels that send blood to the lungs, and a heart arrhythmia called atrial fibrillation.

“We resolved one important question: Can we give testosterone to men with androgen deficiency to try to help them without harming them?” said Dr. Steven Nissen, the study’s senior author and a cardiologist at Cleveland Clinic. “And the answer is, ‘yes.’”

True hypogonadism involves low testosterone levels as well as symptoms and often has a clear cause, such as a genetic syndrome, chemotherapy, head trauma or a pituitary tumor, Dr. Anawalt said.

The study’s findings were presented Friday at the annual meeting of the Endocrine Society in Chicago, and published in the New England Journal of Medicine. Though the trial was carried out by the Cleveland Clinic Coordinating Center for Clinical Research and a contract research organization, it was funded by pharmaceutical companies that make testosterone, at the behest of the Food and Drug Administration.

The study does not resolve all of the safety questions that have dogged testosterone for decades, however. The clinical trial did not include the kind of older men who have been flocking to anti-aging centers. Many of those centers prescribe testosterone, often without testing hormone levels, according to the F.D.A. Only patients with a clear diagnosis of testosterone deficiency based on repeated tests, and with symptoms of deficiency, were included.

Long-term data is also still lacking, and the trial's retention rate was low, with 60 percent of patients in each group discontinuing use of the patch before the end of the trial.

Researchers took steps to account for these limitations, but said that shortcomings remained.

“This was not a perfect trial, and it does not definitively answer the question for all time — and certainly not for patients who are different from those in the study,” Dr. Nissen said, in a pointed reference to men who take testosterone without a diagnosis of hypogonadism.

But the trial's results provide important information for physicians and patients who have hypogonadism, because many physicians, and patients, may have been reluctant to treat the condition because of concerns about heart disease.

“This allows practitioners who were treating patients with hypogonadism to be able to have less concerns about whether there is cardiovascular risk that will outweigh any benefit, and be more focused on which patients are likely to benefit from testosterone replacement,” said Dr. Michael Lincoff, the study's lead author, who is also at the Cleveland Clinic.

Other investigators are analyzing the data to determine how effective testosterone treatment is at alleviating the symptoms of hypogonadism, which include depression, osteoporosis, anemia, loss of muscle mass and a bothersome condition called benign prostatic hypertrophy, which blocks the flow of urine, in addition to sexual symptoms.

The Food and Drug Administration has approved testosterone products only for men whose low testosterone levels are caused by a medical condition like hypogonadism, but doctors are allowed to use medications for other “off-label” purposes.

The agency reviewed testosterone replacement therapy in 2010 after a clinical trial of the hormone was halted when patients taking it started having heart attacks, and in 2015, the F.D.A. required the makers of testosterone to conduct a clinical trial to evaluate the risk.

The agency also added a so-called black box label to testosterone products, warning about a possible increased risk of heart attacks and strokes.

Dr. Shalender Bhasin, an endocrinologist at Brigham and Women's Hospital in Boston who is a co-principal investigator of the study, is analyzing the trial's results to see if testosterone therapy truly improves sexual function and resolves other symptoms of hypogonadism.

“The folklore is that testosterone improves sexual function, but even in that area there are only three or four randomized trials, and most were only of three to six months' duration,” he said, noting that there was a “substantial placebo effect on sexual symptoms.”

Dr. Bhasin's studies, which are not yet published, will look at testosterone's effects on the prostate, bone fractures and the progression of diabetes, among others.

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